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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,509	12/05/2003	Hong Zhang	ISPH-0803	9823

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,509	ZHANG ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-5-03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the communication filed 12-5-03.

Claims 1-14 are pending in the instant application.

Information Disclosure Statement

The information disclosure statements filed 12-5-03 and 10-31-05 fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. They have been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising the administration of compounds that are 8-50 nucleobases in length and targeted to a nucleic acid molecule encoding BCL2-associated X protein of SEQ ID NO: 17, wherein the compounds specifically hybridize with the nucleic acid molecule of SEQ ID NO: 17 and inhibit the expression of BCL2-associated x protein in vitro and in vivo. The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising these compounds that specifically hybridize and inhibit the expression of SEQ ID NO: 17. The specification discloses antisense oligonucleotides that are 20 nucleotides in length and fully complementary to SEQ ID NO: 17. The specification does not disclose any other sequences, including any sequences with less than 100% identity to the complement of SEQ ID NO: 17 that specifically hybridize and inhibit the expression of BCL2-associated x protein in vitro and in vivo.

The genus of nucleic acids claimed encompasses a myriad of structures (*e.g.* thousands of nucleic acid sequences) and the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure. No common structural attributes identify the members of the claimed genus, and distinguish members within the claimed genus from those outside of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, compounds that specifically hybridize and inhibit the expression of

BCL2-associated x protein in vitro and in vivo. Thus, Applicant was not in possession of the claimed genus.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of BCL2-associated x protein of SEQ ID No. 17 in vitro using fully complementary antisense oligonucleotides of 20 nucleobases, does not reasonably provide enablement for methods of inhibiting the expression of BCL2-associated x protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

The claim is drawn to methods of inhibiting the expression of BCL2-associated x protein in vitro and in vivo comprising the administration of compounds that are 8-50 nucleobases in length that specifically hybridize with the 3'UTR of SEQ ID No. 17, encoding the BCL2-associated x protein.

The state of the prior art and the predictability or unpredictability of the art. Branch and Crooke teach that the in vivo (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." ((See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules in vitro and in vivo (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23, pages 321-342, 2002, especially pages 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches the inhibition of expression of SEQ ID NO: 17 in vitro using fully complementary antisense oligonucleotides of 20 nucleobases in length. Applicants have not provided adequate guidance in the specification, however, toward a method of inhibiting BCL2-associated x

protein expression in vivo using antisense. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition using fully complementary antisense of 20 nucleobases in length as being correlative or representative of the ability to inhibit BCL2-associated x protein expression in vivo using the broad genus of oligonucleotides claimed. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of nucleic acids to appropriate target cells harboring SEQ ID NO: 17 in an organism.

The breadth of the claims and the quantity of experimentation required. The claim is drawn to methods of inhibiting the expression of BCL2-associated x protein in vitro and in vivo comprising the administration of compounds that are 8-50 nucleobases in length that specifically hybridize with the 3'UTR of SEQ ID No. 17, encoding the BCL2-associated x protein. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of compounds that specifically hybridize with the 3'UTR of SEQ ID NO: 17 and inhibit its expression in vivo. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells, and BCL2-associated x protein expression is inhibited in the organism. Since the specification fails to provide sufficient guidance for the method claimed, and since

determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 10, 11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zhou et al.

Zhou et al (J. Biol. Chem. 273 (19): 11,930-11936, 1998) teach antisense oligonucleotides between 8-50 nucleobases in length that specifically target the 3'UTR of SEQ ID No. 17 (see first 6 full paragraphs of the experimental procedures, pages 11,930-11,931). The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the

claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotides disclosed by Zhou et al meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression of SEQ ID No. 17, encoding the BCL2-associated x protein.

Therefore, absent evidence to the contrary, claims 1, 2, 10, 11, and 13 are anticipated by or, in the alternative, obvious over Zhou et al.

Claims 1, 2, 10, 11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Apte et al.

Apte et al (Genomics 16: 592-594, 1995) teach antisense oligonucleotides between 8-50 nucleobases in length that specifically target the 3'UTR of SEQ ID No. 17

(see last full paragraph on p. 592). The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotides disclosed by Apte et al meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression of SEQ ID No. 17, encoding the BCL2-associated x protein.

Therefore, absent evidence to the contrary, claims 1, 2, 10, 11, and 13 are anticipated by or, in the alternative, obvious over Apte et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al and Apte et al as applied to claims 1, 2, 10, 11, and 13 above, in view of Korsmeyer and further in view of Milner et al and McKay insofar as the claims are drawn to compositions and methods of inhibiting the expression of SEQ ID No. 17, encoding the BCL2-associated x protein in vitro comprising administration of a composition comprising an antisense oligonucleotide between 8-50 nucleobases in length that specifically hybridizes with and inhibits the expression of SEQ ID NO: 17 in vitro, which oligonucleotide comprises a phosphorothioate internucleotide linkage, a 2'-O-methoxyethyl sugar moiety and a 5'methyl-cytosine, and which is optionally a chimeric oligonucleotide, and which composition further comprises a colloidal dispersion system.

Zhou and Apte are relied upon as cited in the 102/103 rejections above.

The primary references of Zhou and Apte do not teach the inhibition of expression of SEQ ID No. 17, encoding the BCL2-associated x protein, using antisense oligonucleotides between 8-50 nucleotides, optionally including those targeted to the 3' region of the nucleic acid of SEQ ID NO: 17, nor the incorporation of modified

internucleotide linkages, sugar moieties or nucleobases, nor chimeric antisense oligonucleotides, nor colloidal dispersion systems.

Korsmeyer (6,500,626) teach the inhibition of expression of SEQ ID No. 17, encoding the BCL2-associated x protein, using antisense oligonucleotides (see col. 29 and col. 46, lines 54-56).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro, including in the 5', 3' and stop codon regions of the target gene (See figure 1 on p 538 and figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach colloidal dispersion compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which antisense target the 3' UTR region of a target gene. McKay et al also teach the in vitro inhibition and screening of modulators (*e.g.* of various antisense oligonucleotides between 8-80 nucleobases that specifically hybridize with the target gene).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein (BAX) in vitro, because Milner et al and McKay teach the

ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro, including the 3' UTR region of the target gene of interest, using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases because Milner teaches methods of designing and assessing antisense oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro, and Zhou, Apte and Korsmeyer teach the nucleic acid sequences encoding encoding various isoforms of BCL2-associated x protein, and the various isoforms taught by these authors share a common sequence for the 3' UTR. One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-50 nucleobases which best target and inhibit BCL2-associated x protein expression in order to study this target molecule's role in apoptosis, and its role in pathologies related to aberrant expression of BAX, including such conditions as Parkinson's, Alzheimer's.

One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 8-50 nucleobases) for the in vitro

inhibition of BCL2-associated x protein expression. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have expected that the delivery of modified antisense oligonucleotides to target cells harboring BCL2-associated x protein, which antisense specifically hybridize with the target nucleic acid encoding BCL2-associated x protein (e.g. of the 3' UTR of SEQ ID No. 17), would lead to inhibition of expression of BCL2-associated x protein in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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9-13-06

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